REMARKS

The Office Action

Claims 1-21 are pending in this application. Claims 3, 5-9, 12-15, and 17-21 are withdrawn from consideration. Claim 4, 10-11 and 16 are objected to. Claims 1, 2, 4, 10, 11, and 16 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 1, 2, 4, 10, 11, and 16 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and for lack of enablement. By this reply, Applicant amends claim 1, cancels claims 4 and 10-21, and addresses each of the rejections.

Support for the Amendment

Support for the amendment to claim 1 is found in the specification at, e.g., page 4, lines 3-10, and page 6, lines 18-20.

Claim Objections

Claims 10, 11, and 16 are objected to "because they recite a non-elected embodiment, specifically 'differentiated progeny of USSCs'" (Office Action, p. 2). Claims 10, 11, and 16 have been cancelled. This objection can now be withdrawn.

Claims 4 and 16 are objected to "because they recite a non-elected embodiment, specifically 'smooth muscle'" (Office Action, p. 2). Claim 16 has been cancelled and claim 4 has been amended to remove the term "smooth muscle." The objection to claims 4 and 16 can now be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 2, 4, 10-11, and 16 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner states that the phrase "other than diseases of the connective tissue, bone, or cartilage," which is recited in independent claims 1 and 10, is unclear (Office Action, p. 11; emphasis in original). Applicant has removed this phrase from claim 1 and has cancelled claim 10. Thus, this rejection can now be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1, 2, 4, 10, 11, and 16 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states:

> The skilled artisan cannot fully envision the detailed structure of a broad genus of "unrestricted somatic stem cells" apart from the single disclosed cell population of **adherent, fibroblastoid-shaped cells that are $CD34^-$, $CD45^-$, $CD14^-$, CD13+, CD29+, and CD49e+**, to be utilized in the treatment method as claimed, and therefore conception is not achieved until reduction to practice has occurred.

Applicant has amended independent claim 1 to recite that the USSCs "are negative for the CD14 and CD45 antigens and positive for the CD13 and CD29 antigens and lack expression of hyaluronan synthase." Thus, claim 1 no longer encompasses any unrestricted somatic stem cells (USSCs) but instead covers USSCs that can be readily identified by expression of cell surface antigens and by the lack of expression of a cellular enzyme, the detection of each of which is routine in the field of cell biology.

In addition, Applicant respectfully notes that compliance with the written description requirement only requires Applicant to communicate to those skilled in the art that the claimed

subject matter is intended to be part of their invention (see, e.g., *In re Daniels*, 114 F.3d 1452, 46 U.S.P.Q.2d 1788 (Fed. Cir. 1998); *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 U.S.P.Q. 117 (Fed. Cir. 1985)). As stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987):

> [T]he specification must 'convey clearly to those skilled in the art to whom it is addressed...the information that [the inventor] has invented the specific subject matter later claimed.'

The M.P.E.P. § 2163.02 (Eighth Edition, August 2001) states:

> [A]n objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed."

In applying this standard, the Federal Circuit has held that the specification must convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). Applicant need not limit his claims to the narrowest embodiment disclosed in the specification. *See Cordis Corp. v. Medtronic Ave, Inc.* 339 F.3d 1352, 1365 (Fed. Cir. 2003). Furthermore, "[A]n applicant is entitled to claims as broad as the prior art and his disclosure will allow" (*In re Rasmussen*, 650 F.2d 1212, 1214 (CCPA 1981).

Applicant has plainly met the standards discussed above because Applicant's specification clearly indicates to one of ordinary skill in the art that Applicant discovered USSCs having the characteristics now recited in present claim 1 and their use for treating a cardiac muscle disease. For this reason, the rejection of claims 1, 2, 4, 10, 11, and 16 under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.

Enablement

Claims 1, 2, 4, 10, 11, and 16 are also rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention" (Office Action, p. 5). The rejection is based on (i) the unpredictability of the art, (ii) the amount of direction or guidance provided by the specification, and (iii) the lack of a working example. Applicant respectfully disagrees with the Examiner's conclusion. For the reasons discussed below, present claims 1, 2, 4, 10, 11, and 16 are enabled to their full scope.

35 U.S.C. § 112, first paragraph, "requires a determination of whether the disclosure of the invention, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" (M.P.E.P. § 2164.01). The M.P.E.P. § 2164.01 also states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statue does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

Further, the Federal Circuit held in *Musco Corporation v. Qualite, Inc.* (790, 41 USPQ2d (Fed. Cir. 1954)):

> A patent's specification must set forth "a written description of the invention, and

> of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same". 35 U.S.C. § 112. Section 112 requires only an objective enablement; the invention needs to be sufficiently disclosed through illustrative examples or terminology to teach those of ordinary skill in the art how to make and how to use the invention as broadly as it is claimed. *In re Marzocchi,* 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971). Although some experimentation on the part of the artisan is not fatal, *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941, 15 U.S.P.Q.2D (BNA) 1321, 1329 (Fed. Cir. 1990). (Emphasis added.)

Applicant has satisfied this standard.

General Unpredictability of the Art

The Examiner states that, as of the effective filing date of the application,

> little was known on the existence of an "unrestricted somatic stem cell" population that is capable to differentiate into mesenchymal stem cells, hematopoietic lineage stem cells, neural stem cells and endothelial stem cell in the prior art. There is also a significant skepticism or doubt on the plasticity of adult stem cells reported in the literature at about the effective filing date of the present application (Office Action, p. 6).

To support a conclusion regarding the unpredictability of the subject matter of present claims 1, 2, 4, 10, 11, and 16, the Examiner cites numerous post-filing date publications, which the Examiner alleges suggest that the identification and use of adult stem cells is unpredictable.

Applicant strenuously disagrees with this basis of the rejection and strongly asserts that Applicant's identification of USSCs and the experimental evidence discussed below, which demonstrate that USSCs can be used as described in the specification, remove the unpredictability with regard to the identification and use of adult stem cells. Furthermore, using animal models that are predictive of success in treating disease in humans, Applicant has demonstrated the ability of USSCs to engraft and differentiate into multiple tissue types,

including cardiomyocytes, to engraft and repair cardiac function, and to display immune tolerizing properties. As evidence, Applicant directs the Examiner to the Declaration of Morey Kraus, provided herewith, which, as is discussed in more detail below, states that the methods of the present specification have been successfully used to treat cardiac muscle diseases in three different animal models of cardiac disease (i.e., sheep, rat, and pig models). In each of these models, USSCs engrafted in the heart, differentiated into cardiac tissue (e.g., cardiomyocytes and Purkinje fiber cells), and restored function to damaged cardiac tissue (see, e.g., ¶¶ 3-5 of the accompanying Declaration of Morey Kraus).

None of the references cited by the Examiner suggest that adult stem cells, if identified, could not be administered to treat disease conditions; they only suggest that, when identified, investigation into the properties of adult stem cells (e.g., expansion, stability, engraftment, migration, and differentiation of adult stem cells) would be necessary. In the present case, Applicant has actually demonstrated the ability of USSCs to treat cardiac muscle disease, as is discussed below. Thus, Applicant submits that, the cited references notwithstanding, the method of present claim 1, as presently amended, and claims dependent therefrom, is predictable, and the requirements for enablement under 35 U.S.C. § 112, first paragraph, are satisfied (see M.P.E.P. § 2164.01).

Direction or Guidance Provided by the Specification

The Examiner states that the guidance provided by the specification is insufficient to satisfy the enablement requirement. Specifically, the Examiner states:

Even with the disclosed cell population...[of USSCs], there is no evidence of

> record indicating or even suggesting that this cell population is capable of targeting to the desired tissue site (e.g., the diseased cardiac tissue) from any administering site in a human patient, engrafting, proliferating and differentiating into any resident cells of the targeted tissue in a sufficient number to yield any therapeutic effects for the treatment method as claimed. (Office Action, p. 9.)

Applicant respectfully disagrees.

The present specification provides ample guidance for teaching the skilled artisan how to identify and use USSCs in a method for treating a cardiac muscle disease, as is recited in present claim 1, and claims dependent therefrom. For example, the specification describes the preparation of USSCs from umbilical cord blood in enabling detail (see, e.g., page 16, line 16, through page 17, line 20) and teaches that USSCs are identified morphologically by their fibroblastoid cell shape or immunophenotypically by detecting the presence or absence of cell surface markers, namely the presence of CD13 and CD29 and the absence of CD14 and CD45 (see, e.g., page 4, lines 3-10). The specification states that, once isolated, USSCs can, if desired, be expanded (see page 17, lines 22-27), and USSCs can be prepared for administration using art-known carrier or auxiliary substances (see, e.g., page 7, lines 22-26). Finally, the specification states that USSCs can be administered by local or systemic administration using art-known techniques used for the administration of mesenchymal stem cells (MSCs; see, e.g., page 8, lines 3-26). In addition, the specification clearly teaches that USSCs can be differentiated into muscle tissue. For example, on page 14, lines 9-12, and page 20, line 21, through page 21, line 8, the specification teaches that culturing USSCs in the presence of H5100 media containing various growth factors and supplemental agents produces a change in morphology and the expression of muscle-specific slow-acting myosin (see also Figures 15 and 16 of the specification). Thus, the specification clearly provides ample guidance for one skilled in the art to practice the full scope

of present claims 1, 2, 4, 10, 11, and 16.

As evidence that the specification enables the method of present claims 1, 2, 4, 10, 11, and 16, Applicant directs the Examiner to the Declaration of Morey Kraus, which states that the methods of the present specification have been successfully demonstrated in three different animal models of cardiac disease (i.e., sheep, rat, and pig models). In each of these models, USSCs engrafted in the heart, differentiated into cardiac tissue (e.g., cardiomyocytes and Purkinje fiber cells), and restored function to damaged cardiac tissue.

Applicant first directs the Examiner to ¶ 4 of the Declaration, which states that USSCs demonstrated the ability to express essential markers for cardiac muscle, including, e.g., Csx/Nkx-2.5 (cardiac-specific homeobox protein), GATA4 (GATA-binding protein 4), MYH6 (cardiac muscle myosin-alpha, heavy chain 6), MYH7 (cardiac muscle myosin beta, heavy chain 7), MYL2 (cardiac slow myosin light polypeptide 2), TNNT2 (cardiac troponin T2), ACTA1 (actin alpha-1), MEF2C (myocyte-specific enhancer factor 2C), MEF2D (myocyte-specific enhancer factor 2D), CX43 (connexin 43), and DES (desmin), as demonstrated by reverse transcription-polymerase chain reaction (RT-PCR; see Fig. 1 of the Declaration); the expression of other cardiac-related genes by USSCs was also demonstrated (see Fig. 2 of the Declaration).

Applicant next directs the Examiner to ¶¶ 5 and 5(a) of the Declaration, which state that USSCs demonstrated the ability to engraft and differentiate into cardiac muscle when administered to sheep. The results of this study were published as Kögler et al. (J. Exp. Med. 200:123-135, 2004)), which is a post-filing date reference that describes Applicant's own research using USSCs (a copy of which is enclosed as Exhibit A). Kögler et al. shows that USSCs, when administered by intraperitoneal injection into preimmune sheep, engraft at

multiple different sites in the sheep, including the atria and ventricles of the heart, and express proteins characteristic of cardiomyocytes and Purkinje fiber cells (see Fig. 5 of Kögler et al.). Kögler et al. also indicates that USSCs appear to be nonimmunogenic and may even possess immunosuppressive abilities (see page 133, col. 2). Thus, Kögler et al. clearly demonstrates that, following their administration, USSCs home to cardiac tissue and differentiate into cardiac-specific cells, all with little or no significant immune response. Accordingly, Kögler et al. clearly demonstrates that no undue experimentation is required to perform the method of present claims 1, 2, 4, 10, 11, and 16.

Paragraph 5(b) of the Declaration states that USSCs also demonstrated the ability to engraft and differentiate into cardiac muscle when tested in a rat model of myocardial infarction. Here, human USSCs were administered by intramuscular administration into the epicardium of the rat heart 1-2 hours after ligation of the left anterior descending coronary artery (LAD). Four weeks after administration, USSCs were detected histologically in the cardiac muscle of the treated rats. In addition, the cardiac muscle demonstrated a significant improvement in function, as determined by echocardiography and hemodynamic measurement. As is indicated in Figure 3A of the Declaration, rats treated with USSCs demonstrated a significant improvement in intra-arterial pressure versus rats treated with PBS or fibroblasts; the improvement increased with an increase in the number of USSCs administered (compare "low" versus "high"). The graph shown in Fig. 3B of the Declaration shows that administration of USSCs also resulted in an improvement in the ejection fraction (i.e., the amount of blood pumped out of the left ventricle per heart beat), relative to the ejection fraction in rats not administered USSCs, when determined 28 days following LAD; the increase in ejection fraction correlates with an improvement in

function. Thus, these data further demonstrate the ability of USSCs to home to damaged cardiac tissue, to differentiate into cardiac-specific cells, and to repair damage and restore cardiac function.

Finally, ¶ 5(c) of the Declaration further confirms that USSCs demonstrated the ability to engraft at the site of damaged cardiac tissue, to differentiate into cardiac muscle, and to restore function when tested in a porcine acute/chronic myocardial infarction model. Here, USSCs were directly injected into an infarcted region of a porcine heart four weeks after initiation of the infarct. The infarcted myocardium and implanted cells were studied histologically and by single-photon emission computed tomography technetium 99m sestamibi scans (MIBI) and echocardiography. Engrafted USSCs were detected in the infarct region four weeks after cell transplantation, and the implanted cells improved regional and global function of the porcine heart after a myocardial infarction. MIBI confirmed that the transplanted and engrafted USSCs improved regional perfusion ($P<0.05$) and wall motion ($P<0.05$), as compared to the control animal which did not receive USSCs and exhibited no improvement. In addition, the administration of USSCs resulted in an increase in the ejection fraction ($P<0.01$; see Fig. 4 of the Declaration), as detected by MIBI and echocardiography; the control group did not exhibit this improvement in function. Thus, these data further confirm the ability of USSCs to engraft in a damaged heart, to differentiate to cardiac muscle, and to restore cardiac function.

Applicant submits that the data presented in the Declaration confirm that the methods taught in the specification have been successfully used to treat damage to cardiac muscle. Furthermore, as the Declaration attests, these experiments were performed using techniques taught in the specification (see ¶ 3, of the Declaration). Thus, for the reasons discussed above,

the method of present claims 1, 2, 4, 10, 11, and 16 can be preformed with undue experimentation and present claims 1, 2, 4, 10, 11, and 16 are enabled to their full scope.

Working Example

Finally, the Examiner states that "[t]here is an absence of an example demonstrating that any therapeutic effect has been attained or achieved in any human patient for any disease...using any 'unrestricted somatic stem cells' population" (Office Action, p. 10). Applicant notes that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed...An applicant need not have actually reduced the invention to practice prior to filing" (M.P.E.P. § 2164.02). Thus, for the reasons discussed above, and in view of the data presented in the Declaration of Morey Kraus, Applicant believes that all requirements of 35 U.S.C. § 112, first paragraph, have been met. The rejection of claims 1, 2, 4, 10, 11, and 16 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is requested.

Enclosed is a Petition to extend the period for replying for three months, to and including April 28, 2006, and a check in payment of the required extension fee.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 27, 2006

Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045